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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 442,898	11 18 1999	MICHEL AGUET	P1696R1	6537

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EXAMINER

NICKOL, GARY B

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 12 03 2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/442,898

Applicant(s)

AGUET, MICHAEL

Examiner

Gary B. Nickol Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 10 September 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1,2,4-6 and 23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1,2,4-6 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Request for Continued Examination

The request filed on 9-10-02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/442898 is acceptable and a RCE has been established. Claims 1-2, 4-6, and 23 are pending and are currently under prosecution. An action on the RCE follows.

Rejections Maintained:

Claims 1-2, 4-6, and 23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Caras (WO 96/13518, May 1996) in view of Wang *et al.* (Cell, Vol. 93, pages 741-753, May 29, 1998, IDS) for the reasons of record (see Paper Nos: 12 and 8).

Applicants argue (Paper No. 17, page 2) that the combination of the references is *legally* improper. Applicant's argue that the teachings of the references are fundamentally different in that Wang *et al.* teaches ephrin-B2 binding to the EphB4 receptor, and Caras *et al.* teaches ephrin-A5 binding to EphA receptors. Applicants further argue that Caras has no disclosure whatsoever indicating that ephrin-A5 would be structurally or functionally analogous or similar to any ephrin-B, such as Ephrin-B2. Applicants further argue that Wang *et al.* has no disclosure whatsoever indicating that ephrin-B2 would be structurally or functionally analogous or similar to any ephrin-A, such as ephrin-A5. Applicants further argue that since ephrins A and B have been recognized in the art as two different and distinct classes of ephrins, and further since the cited references themselves provide no motivation for their combination, the combination of Caras and Wang *et al.* is legally improper. This argument has been considered but is not found

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persuasive. It appears that applicants are arguing that there is nothing in either reference to link the two families of Eph receptors, namely EphA receptors and their ligands and EphB receptors and their ligands. However, despite the fact that these molecules are considered fundamentally different, they both elicit effects on angiogenesis. Caras *et al.* teach that antagonists of AL-1 can be used to inhibit, prevent or treat pathological angiogenesis, such as during tumor vascularization (page 29, line 6). As stated by applicant (Paper No. 17, page 2), AL-1 is ephrin-A5, a ligand which binds to EphA receptors. Turning to ephrin-B2 and its receptor EphB4, Wang *et al.* teach (page 749) that "ephrin-B2-mediated interactions are essential for angiogenesis of arteries and veins". Tying this in to EphA receptors, Wang *et al.* teach (page 749, 1st column) that Eph-A-class receptors and their ligands have "also been implicated in angiogenesis", and that "ephrin-A1 has been shown to promote angiogenesis in vivo as well as endothelial chemotaxis" (page 750, 2nd column, 2nd paragraph). Hence, the combination of the two references is legally proper since both references teach that EphA and EphB receptors and their ligands elicit angiogenic effects.

Applicants further argue (Paper No. 17, pages 2-3) that even if the combination of the references were legally proper, the combination would not make obvious the invention claimed in the present application. Applicants argue that Wang *et al.* only showed evidence of the involvement of ephrin-B2/EphB4 at stages of embryonic development and has no disclosure suggesting that antagonists of an EphB receptor, such as EphB4, would inhibit angiogenesis in non-embryonic stages. This argument has been considered but is not found persuasive. First, although Wang *et al.* have not shown specific evidence of the involvement of ephrin-B2/EphB4 in vascularization at non-embryonic stages, the reference as a whole suggests their involvement

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in later stages. For example, Wang *et al.* teach (pages 748, 2nd column to page 789) that most or all embryonic arteries expressed ephrin-B2 and EphB4 at the stages they examined. And, although they were unable to detect expression on yolk sac or trunk endothelial cells of ephrins-B1 and -B3 and their receptors Eph-B1, -3, and -A4, the authors stress that such results should not be taken to imply that these are the only ephrins and Eph receptors expressed by arterial and venous endothelial cells *in later development or adulthood*. The authors further point to the fact that **human** renal microvascular endothelial cells have recently been shown to express Eph-B1 and EphB2 as well as ephrin-B1 and ephrin-B2. Hence, it would appear that the authors were not limiting the involvement of ephrin-B2/EphB4 in vascularization solely at embryonic stages.

Secondly, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Moreover, applicant's arguments suggesting that there is no way to extrapolate from embryonic angiogenesis to vascularization at non-embryonic stages is in contrast to applicant's own data which was solely preformed in embryonic stages (See Figure Descriptions for Figures 3A-6, pages 5-6). Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

Conclusion

This is a continuation of applicant's earlier Application No. 09/442898. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
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GBN
November 27, 2002

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